REMARKS

Reconsideration of this application is respectfully requested.

Claims 22, 23, 29 and 30 have been withdrawn from consideration. Claim 26 has been amended. Claims 31 through 34 have been added. Therefore, claims 26-28 and claims 31-34 are pending.

Claim 26 was amended in response to Examiner's rejection under 35 U.S.C. §112, second paragraph. Support for this amendment is found in the specification on page 16, lines 16 through 20, and on page 16, lines 26 through 28.

Support for added claim 31 is found in the specification on page 3, lines 15 through 19; page 56, lines 12 through 16; page 75, lines 13 through 15 and page 76, lines 11 through 23.

Support for added claim 32 is found in the specification on page 46, lines 2-15.

Support for added claim 33 is found in the specification on page 7, lines 5-6.

Support for added claim 34 is found in the specification on page 7, lines 6-8.

I. Formal Objections

A. The Examiner objected to the abstract of the disclosure. In response, Applicants have amended the specification above to substitute a new Abstract in compliance with 37 CFR 1.72. Accordingly, this objection may now be withdrawn.

B. The Examiner required specific reference to the earlier filed co-pending application to be made in the instant application. Accordingly, the specification is amended to insert a reference to a parent application.

II. Rejections Under 35 USC § 112, first paragraph.

A. Claims 26-28 are rejected under 35 U.S.C. §112, first paragraph for lack of written description. Applicants respectfully traverse the rejection. It is known to one skilled in the art that molecules shared by human or mouse in the immune system are also shared among other mammals. To illustrate, Applicants provide two abstracts enclosed herewith in support of this. Full-length articles are being obtained and will be forwarded when they become available. One of these articles (Mehlhop et al., J. Immunological

Methods, 2002, Feb. 1, Vol. 260(2): 219-234) provides evidence that DEC-205 is upregulated on dendritic cells from macaque monkeys following stimulation with monocyte conditioned medium as well as a panel of other known stimulators. Furthermore, the second abstract (Maruyama et al., Cancer Letters, Vol. 181, Issue 2, July 2002, pages 223-232) demonstrates that the multi-domain structure of mouse and human DEC-205 is conserved in hamsters with approximately 80% homology. In light of the foregoing, Applicants respectfully request withdrawal of the rejection.

B. The Examiner further stated that although the claims recite use of a carbohydrate that binds DEC, there is no disclosure in the specification regarding the identity of these carbohydrates. Applicants respectfully traverse this rejection.

Applicants refer the Examiner to a description of carbohydrate ligands that bind DEC on page 38, lines 14-22, where the carbohydrates are defined as glycans, saccharides, or oligosaccharides. Further support for candidate carbohydrate ligands for binding to DEC are described on page 39, lines 22-26. These include mannose, fucose, N-acetyl-glucosamine, glucose, galactose, N-acetyl-galactosamine, disaccharides, and larger order polysaccharides, *e.g.*, such as those recognized by various lectins. Furthermore, it would be apparent to one skilled in the art, as described in the specification on page 39, lines 11-31, and on page 40, lines 1-8, the methods for determining carbohydrate ligands that bind DEC. Based on the foregoing, withdrawal of the rejection is respectfully requested.

III. Rejections Under 35 USC § 112, second paragraph.

A. Claims 26-28 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failure to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

Applicants respectfully traverse this rejection and refer the Examiner to page 16, lines 16 through 20, wherein "DEC" is defined as an integral membrane protein found primarily on dendritic cells, B cells, brain capillaries, bone marrow stroma, epithelia of intestinal villi, and pulmonary airways, as well as cortical epithelium of the thymus and dendritic cells in the T cell areas of peripheral lymphoid organs. Moreover, Applicants have indicated on page 16, lines 26-28 that because the protein has been found

predominantly on Dendritic cells and thymic Epithelial Cells, and has a molecular weight of **205** kDa, it has been termed **DEC-205**. Applicants have also amended claim 26 to better define the DEC protein, as suggested by Examiner. In light of the foregoing, Applicants respectfully request withdrawal of the rejection.

IV. Rejections Under 35 USC § 103(a).

Claims 26-28 are rejected under 35 U.S.C. § 103(a), as being obvious over Nemazee (U.S. patent 5,698,679) in view of Kraal et al. This rejection is respectfully traversed.

The Examiner has the initial burden of establishing a *prima facie* case of obviousness. A finding of obviousness under § 103 requires a determination of the scope and content of the prior art, the differences between the claimed invention and the prior art, the level of ordinary skill in the art, and whether the differences are such that the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. Graham v. Deere, 383 US 1 (1966). Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching or suggestion that the combination be made. In re Stencel, 828 F2d 751, 4 USPQ2d 1071 (Fed. Cir. 1987).

The invention as claimed. The amended claims are drawn to a vaccine for inducing an immune response comprising an antigen from a pathogen conjugated to a Dendritic and Epithelial Cell (DEC)-ligand, wherein the DEC- ligand is selected from the group consisting of a carbohydrate that binds DEC and an anti-DEC antibody, and an immune stimulator

The Nemazee et al. reference as a whole. Nemazee describes peptide/Ig fusion proteins wherein the Ig portion of the fusion protein binds an APC cell surface antigen, the peptide portion of the fusion protein is derived from a virus, an antibody that can bind to the surface of APCs including dendritic cells, and the fusion protein in combination with a lymphokine can be used to immunize an animal.

Nemazee does not disclose or suggest use of the anti-DEC-205 antibody as the antibody which binds a dendritic cell surface antigen.

The Kraal et al. reference as a whole. Kraal et al. describes the monoclonal antibody NLDC-145, which reacts with 145kDa protein found on nonlymphoid dendritic cells, including Langerhans cells, veiled cells, and interdigitating cells, but does not react with cells in the bone marrow and blood.

Kraal et al. does not disclose or suggest that the NLDC-145 antibody reacts with a specific endocytic receptor on dendritic cells and epithelial cells, as well as bone marrow cells, having a molecular weight of 205kDa, characterized as having ten lectin binding domains, and evidence of its role in the uptake and processing of oligosaccharides and oligosaccharide decorated molecules. Kraal et al. does not show that NLDC-145 could bind a receptor that mediates antigen uptake into dendritic cells and antigen presentation by these cells. Moreover, for almost 20 years after Kraal et al., Applicants' discovery of *in vivo* targeting was not carried out, due to failure to recognize and appreciate the problem. It is critical to our invention that DEC-205 be used to target antigens efficiently and selectively to dendritic cells and for purposes of antigen presentation on MHC class I and II products.

The analysis under § 103(a). Kraal et al did not describe the NLDC-145 antibody as being reactive with DEC-205. Moreover, it was not until Applicants' present invention that the identity of DEC and significance as an endocytic receptor became known. Applicants' own work, as described in the instant application, clearly point out that the molecule identified by the NLDC-145 antibody was not a full length, complete DEC molecule. In fact, it was Applicants' own investigative work which identified the discrepancy in the size of the full length DEC molecule as recognized by their own antibodies, compared to the smaller 145kDa protein described by Kraal et al., for which no function was known at the time. Furthermore, Kraal et al. does not describe the binding of NLDC-145 to DEC; they merely identify the binding of a 145kDa protein using their antibody. Nor does Kraal show that NLDC-145 could bind a receptor that mediates antigen uptake into dendritic cells and antigen presentation by these cells. Moreover, for almost 20 years after Kraal et al., Applicants' discovery of *in vivo* targeting was not carried out, due to failure to recognize and appreciate the problem. One cannot contemplate or suggest a solution without recognition of the problem. Thus, the connection between the work done by Kraal et al. could not have been made in light of

the Nemazee patent, since the identity of DEC as an endocytic receptor or a receptor for antigen presentation was unknown at the time.

Furthermore, Nemazee prepares fusion proteins using "peptide precursors" fused to antibody molecules, yet provides no evidence that one can direct this fusion protein to the dendritic cell for vaccine purposes. Furthermore, Nemazee does not provide a method for targeting specifically to an endocytic receptor on the dendritic cell, the primary target of Applicants' invention. Applicants contend that antibodies to any other surface antigen on dendritic cells would not necessarily elicit the appropriate reactivity, uptake and processing needed for eliciting an immune response. Applicants are claiming vaccines prepared through use of a specific targeting mechanism for delivery to the dendritic cell comprising an active receptor for antigen presentation (immune stimulator), the endocytic receptor molecule DEC, and a ligand that binds DEC, which may be either a carbohydrate ligand or an antibody that binds specifically to DEC. Moreover, Nemazee does not envision conjugating the immune stimulatory agent to the fusion protein, as outlined by Applicants in the instant application. Furthermore, Nemazee et al. inserts peptide sequences into the fusion protein in a manner that is very constrained since the CDR region is so short. Applicants' methods allow for long sequences to be fused terminally to the anti-DEC antibody, or complex to be conjugated to the antibody.

It is Applicants contention that Examiner has tried to reconstruct Applicants invention using hindsight reconstruction, which is impermissible.

In light of the foregoing arguments, Applicants respectfully request withdrawal of the rejection.

Conclusion

Applicants believe that the foregoing amendments to the claims place the application in condition for allowance. Withdrawal of the rejections and objections is respectfully requested. If a discussion with the undersigned will be of assistance in resolving any remaining issues, the Examiner is invited to telephone the undersigned at (201) 487-5800, ext. 105, to effect a resolution.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

26. (Amended) A vaccine for inducing an immune response comprising an antigen from a pathogen conjugated to a [DEC] Dendritic and Epithelial Cell (DEC) - ligand, wherein the DEC-ligand is selected from the group consisting of a carbohydrate that binds DEC and an anti-DEC antibody, and an immune stimulator.

ABSTRACT OF THE INVENTION

The identification and characterization of a receptor, designated "DEC" is described, which is associated with antigen presentation in immune responses, endocytosis, and transepithelial transport. DEC is found primarily on dendritic cells, but has been identified on B cells, brain capillaries, bone marrow stroma, epithelial cells of intestinal villi and pulmonary airways, and cortical epithelium of the thymus. The human and murine counterparts of DEC have an apparent molecular mass of 205 kDa, the murine counterpart has an isoelectric point at pH 7.5. Carbohydrates comprise about 7kDa of the total mass of murine DEC. The present invention is directed to the identification of DEC ligands, and the use of DEC-205 to target molecules specifically to dendritic cells and other cells bearing DEC. Targeting antigens for presentation by dendritic cells can provide for tolerance when the dendritic cells are quiescent, or for immune stimulation, when the cells are activated by a cytokine.

1: J Immunol Methods 2002 Feb 1;260(1-2):219-34 Related Articles, Books, LinkO

FULL-TEXT ARTICLE

Enhanced in vitro stimulation of rhesus macaque dendritic cells for activation of SIV-specific T cell responses.

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The macaque-simian immunodeficiency virus (SIV) system is one of the best animal models available to study the role of dendritic cells (DCs) in transmission and pathogenesis of HIV, as well as to test DC-based vaccine and therapeutic strategies. To better define and optimize this system, the responsiveness of macaque monocyte-derived DCs to a variety of maturation stimuli was examined. Characteristic immunophenotypic and functional DC maturation induced by standard monocyte conditioned medium (MCM) was compared to the activation induced by a panel of stimuli including soluble CD40L, LPS, Poly I:C, PGE(2)/TNFalpha, and a cocktail mixture of PGE (2)/TNFalpha/IL-1beta/IL-6. Immunophenotypic analysis confirmed that all stimuli induced stable up-regulation of CD25, CD40, CD80, CD83, CD86, HLA-DR, DC-LAMP (CD208), and DEC-205 (CD205). In general, macaque DCs exhibited weaker responses to LPS and Poly I:C than human DCs, and soluble CD40L stimulation induced variable expression of CD25. Interestingly, while the endocytic capacity of CD40L-matured cells was down-modulated comparably to DCs matured with MCM or the cocktail, the T cell stimulatory activity was not enhanced to the same extent. The particularly reproducible and potent T cell stimulatory capacity of cocktail-treated DCs correlated with a more homogenous mature DC phenotype, consistently high levels of IL-12 production, and better viability upon reculture compared to DCs activated by other stimuli. Furthermore, cocktail-matured DCs efficiently captured and presented inactivated SIV to SIV-primed T cells in vitro. Thus, the cocktail represents a particularly potent and useful stimulus for the generation of efficacious immunostimulatory macaque DCs.

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This Document
▸ **Abstract**
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Hamster DEC-205, its primary structure, tissue and cellular distribution

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Abstract

DEC-205, a putative antigen uptake receptor, belongs to a family of transmembrane C-type lectins. This molecule is known to be one of the most authentic markers for the lineage of dendritic cells. In the present study, we determined the primary structure, tissue distribution and cellular localization of hamster DEC-205. The multi-domain structure of mouse and human DEC-205 was completely conserved in hamster with the overall identity of approximately 80%. DEC-205 transcripts were detected in the thymus and bone marrow cells cultured in the presence of mouse granulocyte macrophage colony-stimulating factor and interleukin-4 in which the DEC-205 expression was up-regulated in the course of cultures. Hamster DEC-205 was mainly detected on cell membrane and shown to mediate the uptake of flourescein isothiocyanate-conjugated ovalbumin. DEC-205 is a highly conserved molecule across the species suggesting its fundamental role in the immune system.

Author Keywords: DEC-205; Antigen uptake; Transmembrane C-type lectin family; Antigen presenting cells

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